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In-Vitro Evaluation of Brand and Generic of Meloxicam Tablets Available in Saudi Arabia

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ABSTRACT

Generic substitution has become a common concern among health care providers, patients and the government. The interchangeability idea raised several concerns related to the safety and efficacy of generics since the late 1970s in the US. In Saudi Arabia, the number of local drug products were increased significantly therefore the need for comparative studies is mandatory. This study aimed to evaluate three meloxicam drug products (15 mg tablets) that are marketed in Saudi Arabia in comparison to the innovator brand (Mobic®, Boehringer, Germany). The physicochemical parameters of meloxicam tablets were assessed according to the united states pharmacopoeia methods including hardness, thickness, uniformity of weight, friability and disintegration tests. Further, the in vivo behavior was predicted and compared by measuring the dissolution rate for all four products. Similarity factor (f2) was used as a quantitative parameter to compare the dissolution curves of the generics with the dissolution curve of the brand. The results of physical evaluations revealed that the four meloxicam products complied with United States Pharmacopeia specifications. The *in-vitro* dissolution performance of the brand and generic products of meloxicam tablets fulfilled the official dissolution rate test limit of NLT 70% in 30 min. Further, based on the calculated similarity factor, no significant differences were observed which indicate possible bioequivalence. In conclusion, the meloxicam generics could be considered equivalent or comparable to the innovator product. However, as meloxicam belongs to class II BCS drug, the interchangeability between these products must be recommended with *in-vivo* bioequivalence studies.

INTRODUCTION:

Generic drug products have a significant impact on countries economic if we look at the price gap between a generic and an innovator's drug. In Saudi Arabia, the substitution of generic drugs costs 16% of the total drug expenses which are estimated to be 4 billion dollars [1]. In the United Kingdom, the replacement of brand products by generic products saving 83 percent of the cost of the product [2]. Nevertheless, a generic drug must be bioequivalent to a brand name in order to describe them interchangeably. A drug considers as generic if it is bioequivalent to a reference or innovator drug in terms of safety, efficacy and dosage form. generic drugs are manufactured without a license after the expiry of all patent rights of innovator drugs [3]. Although, the controversy regarding generic and brand interchangeability is still a debatable point in minds of some health care providers and patients [4]. Published studies in Saudi Arabia [5] and United State [6] demonstrate 17% of physicians prescribed generic medicines in all cases when it is available. In 2007, a study conducted in Greece and Cyprus showed that 51% of physicians in Greece and 60% in Cyprus believe the generics medicines have excellent or acceptable quality [7]. However, only 25% of Greece physicians prescribed generics medicines instead of brand names. Another survey conducted by Toklu et al. in Turkey demonstrated 31% of pharmacists and 32% of physicians believe that generic medicines are effective and safe as an innovator. On the other hand, 40% of pharmacists and 82% of physicians were unconfident about the brand and generic interchangeability [8].

Economic reasons account for the use of generic products more than original drug products. Thus, bioequivalent studies are essential during the development of new medicines. Bioequivalence is defined as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study" [3].

The introduction of the term biowaiver gives the chance to use a dissolution study under certain criteria and specifications to save the time and the money that will consume by in vivo bioequivalent study [9, 10].

Several factors, including physicochemical characteristics of a drug and dissolution rate, have an influence on active ingredients release from dosage forms. Blagden et al. [11] and Grau et

al [12] prove that, the dissolution rate of pure drugs affects significantly by the selection of formulation as well as the processing method. Further, solubility and membrane permeability consider as major factors that affect the in vivo performance of oral solid dosage form. Based on these two factors, Amidon et al reported in 1995 [13] that biopharmaceutics classification system (BCS) categorizes drug substances into four categories which are:

• Class I: high solubility/high permeability

• Class II: low solubility/high permeability

• Class III: high solubility/low permeability

• Class IV: low solubility/low permeability

Class I and III have no issue with dissolution because of their high solubility properties. On the other hand, the dissolution of class II is a limiting step of the absorption process due to the low solubility of drugs in this class such as Meloxicam.

Meloxicam belongs to the non-steroidal anti-inflammatory drugs (NSAIDs) class with high selectivity characteristic toward cyclooxygenase 2 (COX-2) inhibitor. It has many indications in reducing pain and inflammations with less gastric irritation compare to other NSAIDs. It's used in rheumatoid arthritis and osteoarthritis [14]. Since meloxicam is classified as class II based on BCS, the rate of dissolution is very low in biological fluid due to its solubility. In order to improve the solubility, we have to increase the surface area of the drug. Such methods like size reduction, solid dispersion or co-grinding seem effective. Further, the disintegration time of the tablet also affects the dissolution rate of a drug [15].

Meloxicam is available in the Saudi market in several generic products such as Neoxicam®, Oximal® and Coxicam®. Nevertheless, no local studies were conducted to evaluate the physicochemical characteristics and dissolution profiles of these generics compare to the innovator (Mobic®). In recent times, dissolution studies were used to evaluate the performance of generic medicines compare to brand names [16]. Unoriginality, there are no economic studies about money-saving which can be achieved with generics substitution that measured by comparing the retail prices of these products.

The objective of the present study was to make a comparative evaluation of four meloxicam drug products (one brand Mobic®, Boehringer and three generics Neoxicam®, Oximal® and

Coxicam®) to find the interchangeable generic with the brand. The brand and generic products of meloxicam tablets 15mg were evaluated based on physical parameters and in vitro dissolution profiles as per USP methods [17]. The dissolution parameters of the four products were compared by using similarity factor (f2).

MATERIALS AND METHODS:

MATERIALS:

Meloxicam was purchased from UFC Biotechnology USA, Meloxicam tablets having a label strength of 15mg of four different brands were purchased from local pharmacies in Saudi Arabia. The products were coded as A (Mobic®, Boehringer); B (Neoxicam®); C (Oximal®) and D (Coxicam®). The batch number for the products is illustrated in table 1. All chemicals used were of analytical grades. All tests were performed within product expiration dates.

APPARATUS:

The apparatuses used were Gr200 Analytical Balance, Disintegration Tester -Dis.3- (Pharma, Germany), Dissolution Tester (Electrolab, France), Friabilator (Erweka, Germany), Hardness And Thickness Tester (Electrolab, France), and UV Spectrophotometer -UV1800- (Shimadzu, Japan).

Table No. 1: brand and generic of meloxicam products

Groups	Treatment	Batch No.
A	Mobic (Brand)	97-68-73
B	Neoxicam (Generic 1)	08-584-7
C	Oximal (Generic 2)	07-171-61
D	Coxicam (Generic 3)	04-225-127

METHODS:

Hardness test

Sample tablets (6) of each drug product were taken, a tablet was determined by Erwerka hardness tester machine. The pressure was applied on the tablets until it breaks, and the average force of fracture (±SD) was recorded in terms of Kg/cm^2.

Tablet thickness

The thickness of 6 tablets was determined using a micrometer. The mean of thickness (±SD) was calculated.

Uniformity of weigh

Twenty tablets of each brand were weighed together then the average weight was calculated. After that, each tablet was weighed individually by using Gr200 analytical balance, and the deviation percentage and average weight (±SD) were determined.

Friability Test

Ten tablets of each brand were randomly selected and de-dusted then weighed. The tablets loaded in a friability tester and rotated for 100 revolutions at 25 rpm. Then, the tablets were removed from the machine and de-dusted then it was accurately weighed. The percentage of weight loss was calculated using the following formula:

$$\% \text{ Friability} = [(W1-W2) \times 100] / W1$$

Where: W1 = weight of tablet before test (initial weight).

W2 = weight of tablet after test (final weight).

The results should be less than 1 % (USP 2008)

Disintegration time test

The disintegration time of each of the fourth brands was determined at 37 ± 0.5ºC in distilled water as a disintegrating medium using a Disintegration Tester -Dis.3- (Pharma, Germany) apparatus. The mean time (±SD) required the 6 tablets of each brand to be completely dispersion though the mesh was calculated.

Dissolution Rate Study

The dissolution rate of meloxicam from various products of meloxicam tablets was studied using Type II dissolution apparatus according to USP 32 [17]. Tablet from each brand was placed in a vessel containing 900 ml of phosphate buffer pH = 7.5 as dissolution fluid. The dissolution test was performed at 75 ± 1 rpm and the temperature of dissolution fluid is

maintained at 37 ± 0.5ºC. 5 ml sample aliquots were withdrawn at 5, 10, 15, 20, 25 and 30 minutes with medium replacement, simultaneously. Then, sampling was performed after 10 minutes intervals for 60 minutes. All samples were filtered through 0.45 µm membrane filter. The drug amount dissolved of different brands was revealed spectrophotometrically in UV Spectrophotometer -UV1800- (Shimadzu, Japan) at 362 nm. Three tablets randomly selected of each drug products were studied to obtain accurate results.

Similarity factor calculation

The dissolution profile of each generic was compared with the brand name (Mobic®) using f2 (similarity factor) as described by the US FDA [22, 23] and presented in the following equation:

$$F2 = 50\log \{[1 + 1/n\sum^{n=1}(Rt - Tt)^2]^{-0.5} \times 100\}$$

Where Rt is the dissolution value of the innovator brand at time t, Tt is the dissolution value of test products at time t, and n is the number of time points. If the f2 value of generic is equal or greater than 50 and less than 100, it considered similar or bioequivalent to the innovator brand. On the other hand, if f2 value not between 50 and 100, the dissolution curve considered not equivalent hence not interchangeable [9, 18].

RESULTS AND DISCUSSIONS:

Meloxicam is a widely prescribed Nonsteroidal anti-inflammatory drug with analgesic, antipyretic and anti-inflammatory effects [19]. Several brand and generic of meloxicam tablets are available in the world market leading to confusion of their quality and price. The objective of our study is to make a comparative evaluation of four meloxicam drug products (one brand and three generics). The drug products used were within their shelf life at the time of study. The brand and generic products of meloxicam tablets were evaluated for various physical parameters and in vitro dissolution rate as per official methods.

The physicochemical characteristics of meloxicam products tested such as weight variation, hardness, thickness, friability and disintegration time were presented in Table 2. As such all four drug products were within acceptable limits of USP.

All tablets passed weight variation test according to the USP standards (tablet weight varied between 130 – 324 mg should not deviate by ±7.5%) and this mean that all the tablets in the

batch are within reasonable limits and this indicates a good mixing of disintegrates, excipients and active ingredient. The weight of Mobic was varied between 178 and 187 mg, Oximal 178-194 mg, Neoxicam 221-226 mg and Coxicam 203-210 mg. Neoxicam showed the highest average weight compare to the brand and the other generic products. The thickness of all products met the pharmacopeia specifications (none of the drug products deviated by up to ±5% from the mean value) and it was in the range between 2.64 to 3.6 mm with low stander deviation which indicates a good manufactured. The hardness varied between 3.55 and 11.06 Kg/cm2. The average force required to crush the tablets for each brand showed that the hardness for Oximal and Coxicam are less hard compare to the brand and the energy required to break the Neoxicam tablet is harder than the brand which is twice the force required for Mobic (brand). Moreover, the low hardness of Oximal might explain the rapid disintegration although the dissolution profile is not in parallel with the rapid disintegration of the product. However, all the generic and brand products indicating a good mechanical strength to handling when it was the packaging, shipping or deal with other processing. The result of tablet friability test of meloxicam products demonstrated that virtually all the drug products (Mobic, Oximal, Neoxicam and Coxicam) tested had impressive friability values ranging from 0.00% to 0.55%. According to USP no product should have a friability value greater than 1.0%, therefore, all drug products met USP specification. Friability is closely related to the hardness of the tablet and is designed, like the hardness test, to evaluate the ability of the batch to withstand abrasion in packaging, shipping and handling. It's noteworthy that Oximal and Coxicam had less crushing strength compare to other products. Thus, the friability percentage of these two products was higher than Mobic and Neoxicam. Further, the tablets with less hardness (Oximal and Coxicam) had rapid disintegration compare to the others. Our findings were not in agreement with the previous study conducted on meloxicam tablets which revealed that no relationship between the hardness and the disintegration time [20]. Theoretically, high force of compression might prolong the disintegration time and our data support this hypothesis. In general, the disintegration time varied between 1.6 and 4.89 min. The results of a study conducted by Al-kotaji et al in 2019 reported that the dissolution profile of meloxicam tablets was not in parallel with the disintegration time of the tablets which is in agreement with our data and this is might explained by the low solubility of meloxicam [20].

Table No. 2: This is a table. Tables should be placed in the main text near to the first time they are cited

Products	Weight (mg ±SD)	Thickness (mm ±SD)	Hardness (Kg/cm^2 ±SD)	Friability (%)	Disintegration time (minute ±SD)
Mobic	183.85 ± 2.25	2.92 ± 0.03	6.39 ± 0.8	0.00	4.89 ± 0.12
Oximal	183.15 ± 4.6	2.64 ± 0.09	3.55 ± 0.91	0.55	2.03 ± 0.24
Neoxicam	222.7 ± 1.69	3.6 ± 0.04	11.06 ± 1.07	0.00	4.12 ± 0.32
Coxicam	206.45 ± 2.33	3.54 ± 0.09	4.96 ± 0.63	0.44	1.6 ± 0.38

SD = Standard Deviation.

In-vitro dissolution test is one of the important analytical methodology to ensure the quality of one batch to others consistency and to predict in vivo drug release as well [21]. The dissolution rate of meloxicam tablets was studied in a phosphate buffer of pH 7.5 as prescribed in USP 2008. Variations were observed in the dissolution profiles of the four products tested. Table 3 summarizes the characteristics of the four meloxicam products and Mobic was taken as the reference product.

According to a monograph in United States Pharmacopoeia [17], for each of the meloxicam tablets tested for dissolution, the amount of active ingredient of the tablets in solution is not less than 70% of stated amount (15mg for meloxicam tablets) within 30 minutes. Table 3 summarizes the mean percent of drug released at each time pion, the standard deviation (SD) and the upper and lower limits. The results obtained from table 3 revealed that all the meloxicam products passed USP specification for dissolution rate test for conventional release tablets. Further, dissolution curves indicated the analyzed drug products presented similar dissolution profiles Figure 1. Although, Oximal showed a higher dissolution rate than the brand and the rate for the other generics was slightly lower than the brand.

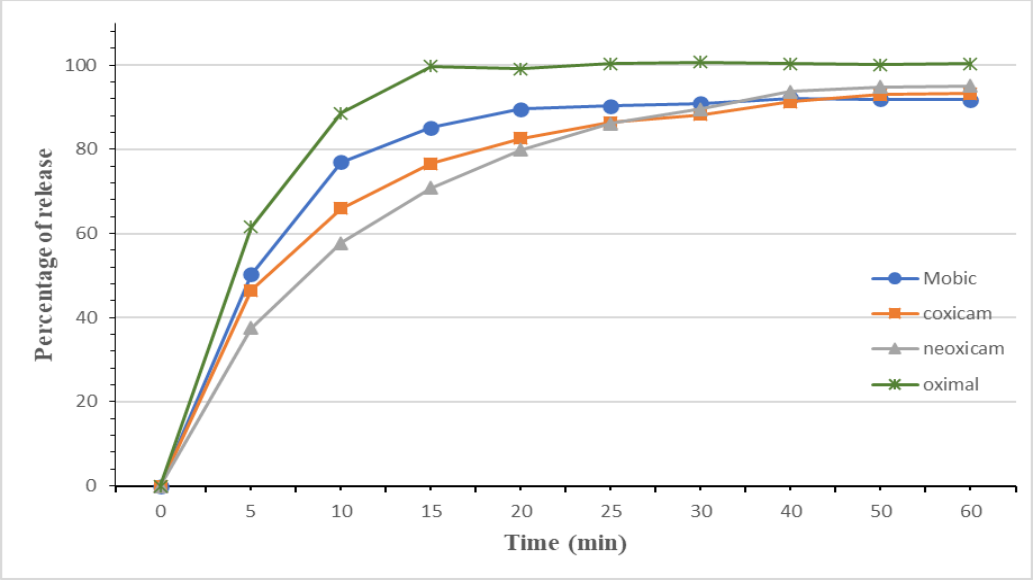

Figure No. 1: dissolution profiles of meloxicam tablets

The similarity factor (f2) is an important quantitative parameter recommended by the FDA to compare dissolution profiles [22]. The results obtained with each generic using the brand as reference are shown in table 4. Based on this assessment all generics had f2 values greater than 50 and therefore can be compared with the innovator brand.

Meloxicam is classified according to the biopharmaceutical classification system (BCS) as a Class II drug therefore not qualified for biowaiver. Moreover, the dissolution test may be formulation-dependent, and the decision related to the interchangeability of the generic products must be made based on the in vivo bioequivalence studies. However, our findings from previous work conducted on rats by using hot plate and formalin tests support our results in this study which are the generics proved to be as good as the brand [4].

Table No. 3: Dissolution rates and descriptive statistics of Meloxicam products

Time (min)	Products	Drug released (%)	SD	Lower limit	Upper limit
5	Mobic	50.31	4.46	46.84	55.34
	Oximal	61.53	12.21	53.44	75.58
	Neoxicam	37.60	6.44	30.19	41.82
	Coxicam	46.51	21.30	30.41	70.66
10	Mobic	76.96	7.29	68.53	81.28

	Oximal	88.57	3.88	85.42	92.91
	Neoxicam	57.72	6.25	52.43	64.62
	Coxicam	65.93	23.95	43.60	91.23
15	Mobic	85.16	6.75	77.59	90.56
	Oximal	94.76	7.56	91.68	106.66
	Neoxicam	70.84	12.55	56.80	80.94
	Coxicam	76.55	20.80	55.68	97.27
20	Mobic	89.52	5.84	82.84	93.69
	Oximal	96.83	8.16	93.80	108.56
	Neoxicam	79.90	11.52	67.30	89.89
	Coxicam	82.55	16.67	64.84	97.94
25	Mobic	90.26	4.00	85.86	93.69
	Oximal	99.36	8.75	95.25	110.46
	Neoxicam	86.12	9.26	75.80	93.69
	Coxicam	86.35	13.04	72.00	97.49
30	Mobic	90.97	2.52	88.43	93.47
	Oximal	100.13	6.03	95.81	107.44
	Neoxicam	89.52	7.72	80.83	95.59
	Coxicam	88.21	10.72	76.25	96.93
40	Mobic	92.09	1.59	90.67	93.80
	Oximal	100.29	5.72	96.71	106.88
	Neoxicam	93.73	5.85	87.09	98.16
	Coxicam	91.30	7.39	82.84	96.48
50	Mobic	92.73	2.11	90.22	94.25
	Oximal	100.80	5.94	96.48	106.99
	Neoxicam	94.88	3.53	90.89	97.60
	Coxicam	93.02	5.51	86.87	97.49
60	Mobic	93.42	0.81	91.23	92.68
	Oximal	100.40	5.44	96.82	106.66
	Neoxicam	95.07	2.56	92.12	96.71
	Coxicam	93.20	3.03	89.89	95.81

SD = Standard Deviation

Table No. 4: The similarity factor of the generic products in comparison to the innovator product

Products	Similarity factor *(f2)*
Neoxicam	52.35
Coxicam	62.19
Oximal	53.58

CONCLUSIONS:

This study concluded that the physicochemical characteristics of the four meloxicam products (Mobic®, Neoxicam®, Oximal®, and Coxicam®) commercially available in Saudi Arabia met the USP specifications. The in vitro dissolution profiles of the brand and generic products of meloxicam tablets fulfilled the specifications (NLT 70% in 30 min) that established by the USP also there are no significant differences observed based on the calculated similarity factor (f2). Thus, the generics could be considered equivalent or comparable to the innovator product. However, as meloxicam belongs to class II BCS drug, the interchangeability between these products must be recommended with *in-vivo* bioequivalence studies.

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REFERENCES:

1. Gamble P. Saudi Arabia's 2012 budget. Jadwa Investment. 2011;26:9.

2. Kamerow D. The pros and cons of generic drugs. BMJ. Jul 20 2011;343:d4584. doi:10.1136/bmj.d4584

3. Food and Drug Administration. U.S.D.o.H.a.H.S.F.a.D.A. Guidance-for-Industry-Bioavailability-and-Bioequivalence-Studies-for-Orally-Administered-Drug-Products---General-Considerations, Editor. 2002: file:///J:/!GUIDANC/4964dft.doc.

4. Alshehry. YA, Ghonaim. HM, Khalid. MS. Comparative Evaluation of the Analgesic Effect of Brand and Generics of Meloxicam tablets Available in markets. International Journal of Pharmaceutical and Phytopharmacological Research. 2019;9(3):73-79.

5. Alghasham AA. Generic drug prescribing in central Saudi Arabia: perceptions and attitudes of physicians. Ann Saudi Med. Jan-Feb 2009;29(1):24-9. doi:10.4103/0256-4947.51819

6. Barrett LL. physicians' Attitudes and Practices Regarding Generic Drugs.pdf. Washington DC, AARP Knowledge Management. 2005;

7. Theodorou M, Tsiantou V, Pavlakis A, et al. Factors influencing prescribing behaviour of physicians in Greece and Cyprus: results from a questionnaire based survey. BMC Health Serv Res. Aug 2009;9:150. doi:10.1186/1472-6963-9-150

8. Toklu HZ, Dülger GA, Hıdıroğlu S, et al. Knowledge and attitudes of the pharmacists, prescribers and patients towards generic drug use in Istanbul–Turkey. Pharmacy practice. 2012;10(4):199.

9. Food and Drug Administration. W.o.I.V.B.a.B. Studies and G.f.I. for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, Editors.: www.FDA.gov. (accessed online 30-05-2020).

10. Mishra V, Gupta U, Jain NK. Biowaiver: an alternative to in vivo pharmacokinetic bioequivalence studies. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2010;65(3):155-161.

11. Blagden N, de Matas M, Gavan PT, York P. Crystal engineering of active pharmaceutical ingredients to improve solubility and dissolution rates. Adv Drug Deliv Rev. Jul 30 2007;59(7):617-30. doi:10.1016/j.addr.2007.05.011

12. Grau MJ, Kayser O, Muller RH. Nanosuspensions of poorly soluble drugs--reproducibility of small scale production. International journal of pharmaceutics. Mar 10 2000;196(2):155-9. doi:10.1016/s0378-5173(99)00411-1

13. Amidon GL, Lennernäs H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharmaceutical research. 1995;12(3):413-420.

14. Kumar SGV, Mishra DN. Preparation and evaluation of solid dispersion of meloxicam with skimmed milk. Yakugaku Zasshi. 2006;126(2):93-97.

15. Engelhardt G, Homma D, Schlegel K, Utzmann R, Schnitzler C. Anti-inflammatory, analgesic, antipyretic and related properties of meloxicam, a new non-steroidal anti-inflammatory agent with favourable gastrointestinal tolerance. Inflammation Research. 1995;44(10):423-433.

16. Rocha-Alcaraz MF, Torres-Sánchez ED, Torres-Jasso JH, et al. In vitro dissolution characteristics of patent, generic and similar brands of naproxen in various dissolution media. Tropical Journal of Pharmaceutical Research. 2019;18(6):1155-1160.

17. United States Pharmacopeia (USP) and the National Formulary (NF). 32th ed. U.S; 2008:2873.

18. Moore JW, Flanner HH. Mathematical comparison of dissolution profiles. Pharmaceutical technology. 1996;20(6):64-74.

19. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. Jun 23 1971;231(25):232-5. doi:10.1038/newbio231232a0

20. Al-kotaji M. Comparative study of different meloxicam generic products with the brand product. Al-Mustansiriyah Journal for Pharmaceutical Sciences. 2019;19(4):116-124.

21. Dressman JB, Amidon GL, Reppas C, Shah VP. Dissolution testing as a prognostic tool for oral drug absorption: immediate release dosage forms. Pharmaceutical research. 1998;15(1):11-22.

22. Food and Drug Administration. Guidance for Industry, Testing of Immediate Release Solid Oral Dosage Forms. U.S. Department of Health and Human Services, Center for Drug Evaluation and Research (CDER), (U.S. Government Printing Office: Washington, DC.) (1997).

23. Oliveira É de FS, Azevedo R de CP, Bonfilio R, Oliveira DB de, Ribeiro GP, Araújo MB de. Dissolution test optimization for meloxicam in the tablet pharmaceutical form. Braz J Pharm Sci. 2009;45(1):67-73.